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# SYNTHETIC STUDIES TOWARD MARINE TOXIC POLYETHERS (1)

## A STEREOCONTROLLED SYNTHESIS OF THE C-SEGMENT OF OKADAIC ACID

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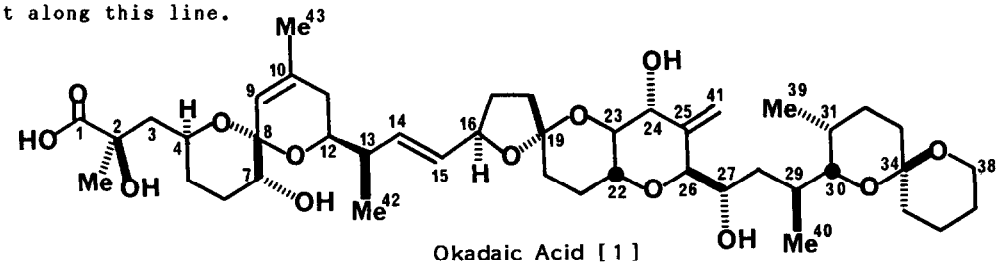
Abstract: Okadaic acid was antithesized into three segments A, B and C, and this paper deals with the synthesis of the C-segment in the form of **24**, which was prepared in 16 steps from a D-glucopyranose derivative (**11**) via the lactone **18**. The key step is the introduction of the C-29 asymmetric carbon via hetero-conjugate addition at neighbouring spiro ethers.

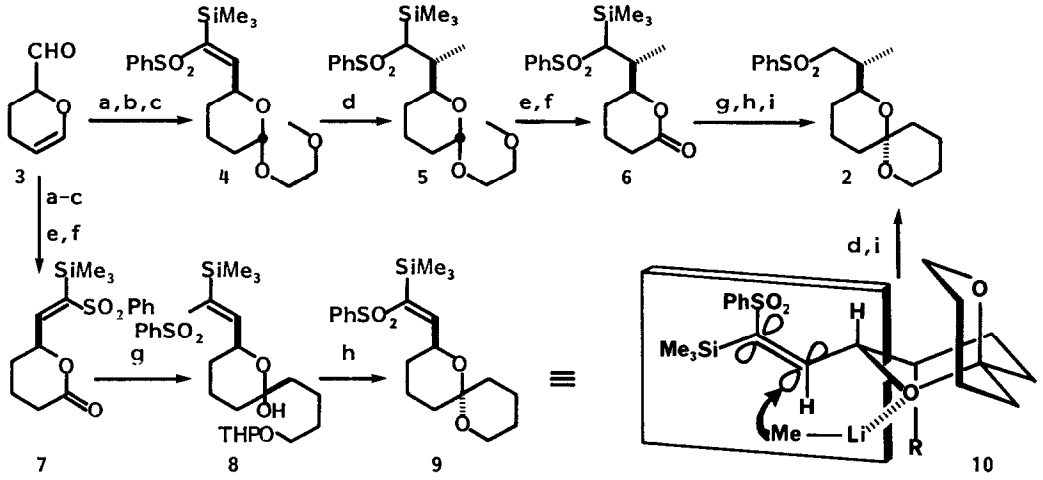
Okadaic acid (**1**, $C_{44}H_{68}O_{13}$, MW 804) which is produced by Halichondria okadai, Dinophysis fortii, etc., possess unique antitumor activity accompanied by strong toxicity. It occurs as the shellfish toxin along the coast of Japan.[1] The structure was elucidated by X-ray crystallographic analysis as **1** that is a carboxylic acid with continuous 38 carbon atoms. It involves 17 chiral centers four of which are on the acyclic parts. The synthetic strategy toward **1** involves (i) retrosynthetic disconnection into three segments (A, B and C) at two bonds (C14-C15 and C27-C28), (ii) synthesis of all the segments in optically active form and (iii) coupling the segments C with B and then with A. This paper deals with the stereocontrolled synthesis of the C-segment along this line.




Okadaic Acid [ 1 ]

The C-segment contains a chain with 11 carbons through C28 to C38 with four asymmetric centers at C29, 30, 31 and 34. Crucial synthetic step is stereocontrol for the asymmetric carbon (C29) at the acyclic position, and this problem will be solved by heteroconjugate addition[2] for syn-diastereoselection from the C-30 asymmetric carbon. In case of the stereoselection for the spiro-ketal carbon (C-34), it will be oriented by its thermodynamic nature known as annomeric effect.[3] These respects were first confirmed in a model study on the racemic spiro compound **2**, which was synthesized from acrolein-dimer (**3**) via the known heteroolefin **4** in two routes shown in Scheme 1.[2b] Addition of MeLi to **4** produced **5** (100% syn-isomer), which was further treated with $H_3O^+$

and aq. bromine in NaOAc/HOAc at pH 5 to produce the lactone **6**. Grignard reaction and subsequent treatments with acid and fluoride gave the spiro derivative **2** in 53% yield. Meanwhile, the spiro-heteroolefin **9** was prepared in two steps (47%) from the lactone-heteroolefin **7**, in which heteroolefin was less reactive to the Grignard reagent than the lactone carbonyl. Addition of MeLi to **9** occurred in a 95% syn-selectivity (in 82% yield) to give, after desilylation, **2**, which was stereochemically identical with the authentic **2** prepared via **5**. The cmr of the C40 and C34 of **2** appeared at $\delta$ 14.9 and 95.5 ppm, respectively, indicating **2** to have the right stereochemistry.[4] The acyclic stereo-control in the introduction of the syn-methyl was designed so that the MeLi can attack selectively due to the conformational and chelational control at the transition state of the spiro system such as **10**.

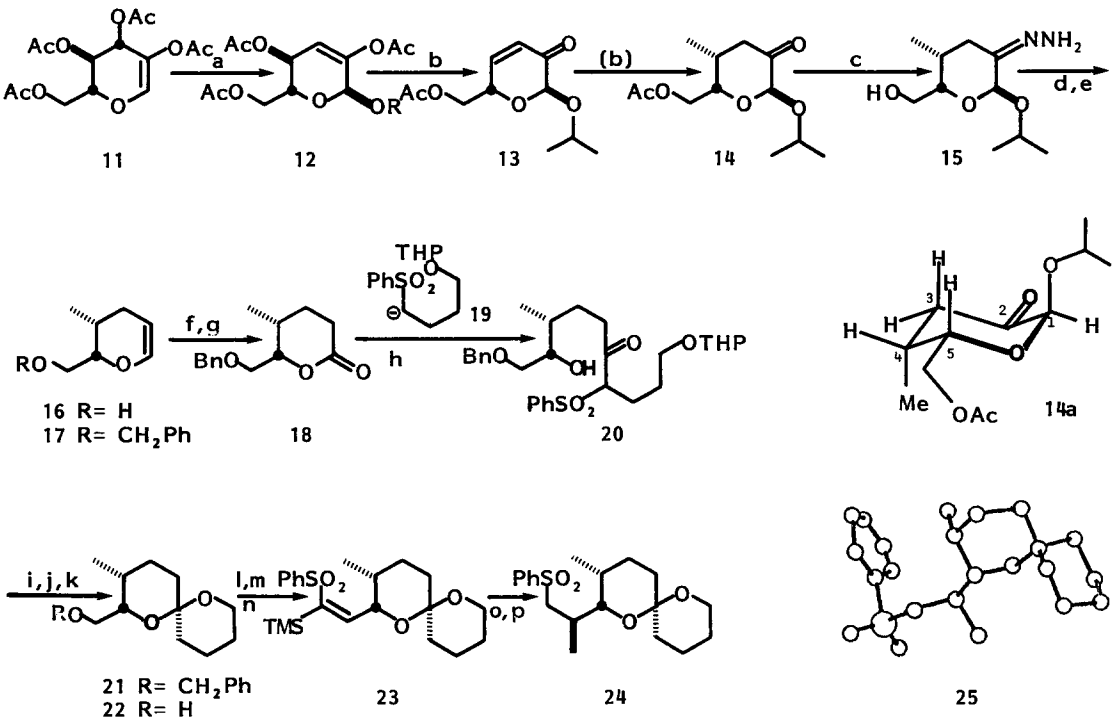



**Scheme 1**

(a) $PhS(TMS)_2CLi$; (b) $HOCH_2CH_2OCH_3$, $H^+$; (c) MCPBA; (d) MeLi; (e) 0.5N HCl (f) $Br_2$; (g) $ClMgCH_2CH_2CH_2CH_2OTHP$; (h) PPTS/EtOH; (i) KF

Synthesis of **24** was planned in the optically active form from a D-hexopyranose. 2-Acetoxy-D-glucal **11**, preparable from glucose in two steps, was treated with i-PrOH in dry benzene in the presence of $BF_3$-$Et_2O$ at rt for 15 min under $N_2$ to afford **12** [R= i-Pr, mp 61°C, $[\alpha]_D$ = +93.7° (c= 1.00, $CHCl_3$)] in 63% yield.[5] To a solution of Me(CN)CuLi was added a solution of **12**[6] [R=i-Pr] in THF at -20°C, while it was converted to the enone **13** and further to **14** by a completely axial Me-attack. The ketone **14** was obtained in 80% yield[7] [$[\alpha]_D$= +158° (c=1.03, $CHCl_3$), 1735 cm-1, $J_{3,4}$= 6 and $J_{4,5}$ = 2 Hz (see **14a**)]. Eliminative Wolff-Kishner reduction of the ketone **14** into **16** was achieved in 74% yield by treatment of the corresponding hydrazone **15** at room temperature in DMSO[8] with NaH. After protecting the hydroxyl group as its benzyl-ether **17** was successively treated with a mixturte of 0.3N HCl-THF (1:5) at 55°C for 6 hr to the corresponding hemiacetal and then with bromine and NaOAc in DMF to afford **18**[9] [52% overall yield $[\alpha]_D$ = +31.4° (c=0.9, $CHCl_3$)]. The lactone carbonyl of **18** was alkylated with the mono-anion **19** (3 equiv.) to produce **20** in 86% yield. Reductive removal of the $PhSO_2$ in **20** was effected with Al-Hg

in aq. THF at rt (in 98%) and the treatment of the product with pyridinium tosylate in refluxing EtOH with 2,2-dimethoxypropane for 12 hr produced the spiro-compound **21**,[10] which was hydrogenolyzed with Pd-C/$H_2$ into **22** [$[\alpha]_D$ = +102.4°(c= 0.93, $CHCl_3$)] in 81% yield. Swern oxidation of **22** was followed by Peterson olefination and MCPBA oxidation to produce the hetero-olefin **23** [$[\alpha]_D$ = +4.0° (c=1.09, $CHCl_3$)][11] in 56% overall yield. In this case, Z-heteroolefin was the predominant over the E-isomer, the ratio being ca. 10:1. MeLi was added to the spiro-heteroolefin **23** in THF at -78°C for 15 min and at -30°C for 4.5 hr, and then the syn-adduct was treated with KF in MeOH to give **24** [mp 82.5°C, $[\alpha]_D$ = +21.6°(c=1.21, $CHCl_3$)][12] in 89% yield. The cmr signal of thus introduced Me of **24** appeared abnormally at 17.0 ppm rather than at the empirical value for syn-isomer at about 14 ppm; this may be due to the presence of ring-methyl which affected the conformation of **24**. The stereochemistry of **24** was finally confirmed by X-ray crystallographic analysis as shown in **25**. The overall yield of the synthesis of the C-segment in the form of **24** was 6.6 % in 16 steps from **11**.




**Scheme 2**

(a) i-PrOH, $BF_3$-$Et_2O$; (b) $Me_2CuLi$ or Me(CN)CuLi; (c) $N_2H_4$/EtOH; (d) $NaCH_2SOCH_3$; (e) $PhCH_2Br$/NaH; (f) $H_3O^+$; (g) $Br_2$; (h) n-BuLi; (i) Al-Hg; (j) PPTS/EtOH; (k) Pd-C/$H_2$; (l) $(COCl)_2$/DMSO/TEA; (m) $PhS(TMS)_2CLi$; (n) MCPBA; (o) MeLi; (p) KF

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**References and Notes**


1. a) K. Tachibana, P.J. Scheuer, Y. Tsukitani, H. Kikuchi, D.V. Engen, J. Clardy, Y. Gopichand, F. Schmitz; J. Am. Chem. Soc., **103**, 2469 (1981): b) M. Murata, M. Shimatani, H. Sugitani, Y. Oshima, T. Yasumoto; Bull. Japan. Soc. Sci. Fish., **48**, 549 (1982).
2. a) M. Isobe, M. Kitamura, T. Goto; Tetrahedron Lett., 3465 (1979): b) idem. ibid., **22**, 2391 (1981): c) M. Isobe, Y. Ichikawa, T. Goto; Tetrahedron Lett., **22**, 4287 (1981).
3. P. Deslongchamps, "Stereoelectronic Effects in Organic Chemistry", Pergamon Press, Oxford (1983).
4. Empirical values for the chemical shifts of Me in syn and anti diastereoisomers are about 14 ppm and 17 ppm, respectively.
5. This glycosidation step afforded various corresponding glycosides when treated with MeOH, EtOH, n-PrOH or n-BuOH, but all of the products were non-crystalline and showed less selectivity in the following methyl addition with $Me_2CuLi$. t-Butyl glycoside has been reported in S. Hanessian, P.C. Tyler, Y. Chapleur, Tetrahedron Lett., **22** 4583 (1981).
6. **12**; δ 1.11 & 1.18 (each 3H, d, J= 6), 2.02(9h, S), 3.76(1H, m), 4.00-4.32(3H, m), 5.10(s), 5.3(1H, m), 5.65(1H, d, J= 2).
7. **14**; δ 0.98(3H, d, J= 7), 1.18(3H, d, J= 6), 1.29(3H, d, J= 6), 2.09(3H, s), 2.18(1H, ddd, J= 14, 2, 1), 2.40(1H, m), 3.01(1H, dd, J= 14, 6), 4.01(1H, tt, J= 6, 6), 4.1-4.2(2H, m), 4.60(1H, ddd, J= 7, 5, 2), 4.69(1H, s).
8. Usual Wolff-Kishner reduction condition requires a drastic condition such as heating up to 160°C with KOH to give a mixture of **16** and the corresponding reduced product. On the other hand, DMSO solvent gives only **16**. [See D. Cram, .R. Sahyun, G.R. Knox; J. Am. Chem. Soc., **84**, 1734 (1962)]. The corresponding tosylhydrazone of the ketone **15** was only reduced with catecolborane to give simply reduced product in only 30% yield with several other unidentified products. [See, G. W. Kabalka, J.H. Chandler; Synthetic Commun., **9**, 275 (1979).
9. **18**; δ 0.96(3H, d, J= 6), 1.6-2.1(2H m), 2.2(1H, m), 2.5(2H, AB), 3.5-3.7 (2H, m), 4.4-4.6(3H, m), 8.2-8.4(5H).
10. **21**; δ 0.90(3H, d, J= 7), 1.2-2.0(10H), 2.10(1H, tt, J= 13, 5), 3.4-3.9(4H), 4.05(1H, ddd, J= 7, 6, 2), 4.6(2H, AB), 7.3(5H). cmr δ 11.2, 18.7, 25.4, 26.1, 28.1, 30.3,35.6, 60.4, 70.0, 71.9, 73.3, 95.5, 127.3, 128.2, 138.6.
11. **23**; δ 0.34(9H, s), 0.90(3H, d, J= 7), 2.2-2.9(9H), 2.02(1H, tt, J= 13, 4), 3.00(1H, td, J= 11, 3), 3.26(1H, ddd, J= 11, 4, 2), 4.88(1H, dd, J= 9, 3), 6.48(1H, d, J= 9), 7.2-7.4(3H), 7.8-7.9(2H).
12. **24**; δ 0.68(3H, d, J= 7), 1.26(3H, d, J= 7), 1.3-2.2(12H), 2.84(1H, dd, J= 14, 10), 3.20(1H, d, J= 14, 2), 3.38(1H, dd, J= 10, 2), 3.5-3.6(2H), 7.6(3H), 7.9(2H). cmr δ 10.7, 17.0, 18.7, 25.3, 26.4, 27.5, 30.1, 31.4, 35.7, 58.9, 60.5, 73.2, 95.9, 128.0, 129.3, 133.6, 139.8.


[NMR data were taken in $CDCl_3$ as TMS-internal standard and are expressed in δ ppm(Hz)].

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